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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,897	CARMI ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *72-101* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Election/Restrictions

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

I. Claims 72-76, drawn to an isolated **an isolated enzyme** capable of mediating a site-specific recombination between two predetermined recombination sites, wherein at least one recombination site is an asymmetric recombination site.

II. Claims 77-83 and 85 drawn to an isolated **nucleic acid sequence** encoding an enzyme capable of mediating a site-specific recombination between two predetermined recombination sites, wherein at least one recombination site is an asymmetric recombination site, a vector comprising said nucleic acid sequence and a host cell transformed with said vector.

III. Claim 84 drawn to a **transgenic plant** comprising an isolated nucleic acid sequence encoding an enzyme capable of mediating a site-specific recombination between two predetermined recombination sites, wherein at least one recombination site is an asymmetric recombination site

IV. Claim 84 drawn to **transgenic yeast** comprising an isolated nucleic acid sequence encoding an enzyme capable of mediating a site-specific recombination between two predetermined recombination sites, wherein at least one recombination site is an asymmetric recombination site.

V. Claim 84 drawn to a **transgenic mammal** comprising an isolated nucleic acid sequence encoding an enzyme capable of mediating a site-specific recombination between two

predetermined recombination sites, wherein at least one recombination site is an asymmetric recombination site.

VI. Claims 86-89 and 94-99 drawn to **a method for treating a disease**, comprising: a. providing a composition comprising a DNA molecule comprising a nucleotide sequence encoding at least one enzyme, capable of mediating site-specific excision of a gene fragment flanked between two recombination sites, wherein at least one recombination site is an asymmetric recombination site; b. administering the composition to a subject in need thereof; thereby obtaining site-specific excision of the gene fragment from a predetermined genomic locus, wherein the composition further comprises a carrier operably connected to the isolated DNA molecule, **the carrier capable of targeting said isolated DNA molecule to a cell and promoting internalization of said isolated DNA molecule into the cell**. and said carrier is selected from the group consisting of: viruses, liposomes, lipid/DNA complexes, micelles, protein/lipid complexes, nanoparticles, and microparticles.

VII. Claims 86 and 91-93 drawn to **a method for treating a disease** comprising: a. providing a composition comprising a DNA molecule comprising a nucleotide sequence encoding at least one enzyme, the at least one enzyme is capable of mediating site-specific excision of a gene fragment flanked between two recombination sites at a defined genomic locus, wherein at least one recombination site is an asymmetric recombination site; b. transforming a cell with the composition; and c. proliferating the transformed cells *ex vivo*, wherein the cell is autologous..

VIII. Claims 86 and 100-101 drawn **a method for treating a disease** comprising wherein the composition comprises:(i) **a first DNA molecule**, the first DNA molecule comprises a first recombination site; and (ii) **at least one enzyme** capable of mediating site-specific insertion of the first DNA molecule into a second recombination site within a specific genomic locus, wherein at least one of said first and second recombination site is an asymmetric recombination site thereby obtaining at step (b) a site-specific excision of the gene fragment from a predetermined genomic locus.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical reasons:

37 CFR 1.475 (c) states:

> "If an application contains to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present"

37 CFR 1.475 (d) also states:

> "If multiple products, processes of manufacture, or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT article 17(3)(a) and 1.476(c)".

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical reasons: the technical feature linking groups I-VIII appears to be that they all relate to

compositions and methods for catalyzing asymmetric recombination of non-palindromic recombination sites in a cell free system, in isolated cells or in living organisms. However, prior art has taught Agrobacterium-mediated transfer of T-DNA to a plant cell, wherein the T-DNA contains a viral replicon flanked by recombination sites for a site-specific wild type recombinase, the recombination sites comprising mutant spacer sequences and/or additional restriction sites outside of each palindromic repeat. Recombination by conservative, FPL site-specific recombinase between inverted FRT sites causes inversion of a DNA sequence between them, whereas recombination between directly oriented sites leads to excision of the DNA between them (Baszczynski et al., U.S. Pat. No. 6,664,108). Therefore, the technical feature linking the invention of groups I-VIII does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over prior art for the reasons set forth above.

The inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Inventions of Groups I-VIII are drawn to materially different and distinct inventive concepts, having different chemical structures, physical properties and biological functions. Inventions of **Group II** drawn to a **DNA expression vector** construct comprising sequences encoding an enzyme capable of mediating a site-specific recombination between two predetermined recombination sites are structurally and functionally different from inventions of **Group I** drawn **a protein** with amino acid sequences homologous to an enzyme capable of mediating a site-specific recombination between two predetermined recombination sites as the result of comprising either polynucleotides or polypeptides which require separate searches; they

are not obvious variants and deemed patentably distinct for the following reasons: polynucleotides, which are composed of purine and pyrimidine units and polypeptides/proteins, which are composed of amino acids, are structurally distinct molecules; any relationship between a polynucleotide and polypeptide is dependent upon the information provided by the nucleic acid sequence open reading frame as it corresponds to the primary amino acid sequence of the encoded polypeptide. Moreover, because of the degeneracy of the genetic code, different nucleotide sequences can encode the same polypeptide sequence. Hence, the information provided by a polynucleotide of Group II can be used to make a materially different polypeptide than that of Group I. Moreover, inventions of **Groups III, IV and V** drawn to transgenic organisms including unique technical features that are not shared by the inventions of Groups I or II. For example, many recombinant therapeutic proteins are produced using mammalian expression systems which correctly synthesize and process mammalian products, whereas transgenic plants do not. Moreover, genes isolated form eukaryotic strains my contain introns whereas bacterial genes contain no introns, thus expression of eukaryotic genes in prokaryotic host requires an uninterrupted (intronless) DNA molecule for the construction of a heterologous expression vector in order to avoid the possibility that splice signal residing on the genomic fragment are not recognized in the heterologous host. Furthermore, Groups VI, VII and VIII are drawn to methods comprising materially different and distinct inventive concepts, having different chemical structures, physical properties and biological functions, which require non-coextensive search and examination. For example, Group VIII, drawn to a method for treating a disease, comprises the active step of administering a first DNA molecule and at least one enzyme which steps are not disclosed as required by the inventions of Groups VI and VII. Moreover,

Group VII requires the step of transforming cells with a composition (e.g., *ex vivo*) which active step is not disclosed as required by Groups VI and VIII. Thus, it follows from the preceding analysis that the claimed inventions listed as Groups I-VIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding technical features for the reasons set forth above.

In addition, if any of inventions I -V are elected, a **further restriction** is required between nucleotide sequences and proteins sequences which involve nucleic acid molecules of and corresponding protein sequences **of SEQ ID NOS: 1-34** which are each distinct nucleic acid coding sequences which encode specific and unique polypeptides. The inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: As the technical feature of a nucleotide sequence coding for a polypeptide, linking the members does not constitute a special technical feature as defined by PCT Rule 13.2, particularly since each of the each nucleic acid does not overlap in scope with the others, are not obvious variants, and have materially different functions, the requirement for unity of invention is not fulfilled.

Applicants must elect one specific nucleotide SEQ ID NO encoding a corresponding polypeptide sequence.

MPEP 1893.03(d) states:

> If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any nonelected process claim that requires all the limitations of an allowable process claim, should be rejoined. See MPEP § 821.04 and §

821.04(a). Any nonelected processes of making and/or using an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b).

Species restriction

Should Groups **I or II** be elected, a species restriction is further required under 35 U.S.C. 121 and 372, wherein a species election(s) must correspond to an elected group as indicated above. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

1) (a) **inversion of a first DNA molecule encompassed within a second DNA molecule,**

(b) **excision of a first DNA molecule from a second DNA molecule**,

(c) **insertion of a first DNA molecule into a second DNA molecule**, and

(d) **translocation between a first DNA molecule and a second DNA molecule**, wherein the second DNA molecule is selected from the group consisting of: genomic DNA and circular DNA, as recited in **claim 73.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique site-specific recombination evens with unique step properties and limitations that define the product made that do not extend one to the other.

2) 3' UTRs, 5' UTRs, polyA sites and gene promoters, as recited in **claim 74.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique predetermined

genomic sites with unique step properties and limitations that define the product made that do not extend one to the other.

3) wild recombinase Cre, FLP as recited in **claims 75 and 76.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique recombinant enzymes with unique step properties and limitations that define the product made that do not extend one to the other.

Should Group **II** be elected, a species restriction is further required under 35 U.S.C. 121 and 372, wherein a species election(s) must correspond to an elected group as indicated above. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

4) naked DNA plasmid, a plasmid within a liposome, a retroviral vector, an AAV vector, or a recombinant adenoviral vector, as recited in **claim 77.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in isolated polynucleotide vectors with unique step properties and limitations that define the product made that do not extend one to the other.

5) E. coli *lac* and *trp* operons, the tac promoter, the bacteriophage λL promoter, bacteriophage T7 and SP6 promoters, β-actin promoter, insulin promoter, human cytomegalovirus (CMV) promoter, HIV-LTR, RSV-LTR, SV40 promoter, baculoviral

polyhedron, p10 promoter, tetracycline, heat shock, steroid hormone, heavy metal, phorbol ester, adenovirus E1A element, interferon and serum inducible promoters, as recited in **claims 78 and 79.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in promoters with unique step properties and limitations that define the product made that do not extend one to the other. For example, cytomegalovirus (CMV) immediate-early promoter, simian virus SV40 early promoter and Rous sarcoma virus promoter can drive expression in a wide range of cells and tissues., eg CMV promoter can be activated in nearly all cell types, non-viral promoters such as βactin have general activity within eukaryote cells and insulin promoter are activated specifically islet beta cells.

6) inversion, excision, insertion and translocation, wherein the recombination occurs between the cellular endogenous genome and an exogenous DNA molecule such that the exogenous DNA molecule is integrated by recombination between the two recombination sites into a predetermined locus within the cellular genome, as recited in **claim 82.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique site-specific recombination evens with unique step properties and limitations that define the product made that do not extend one to the other.

7) yeast, plant cell, embryonic stem cell, mesenchymal cell, and haematopoietic progenitor cell, as recited in **claim 83.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique transformed host cells with unique step properties and limitations that define the product made that do not extend one to the other.

Should Groups VI, VII or VIII be elected, a species restriction is further required under 35 U.S.C. 121 and 372, wherein a species election(s) must correspond to an elected group as indicated above. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

8) liposomes, lipid/DNA complexes, micelles, protein/lipid complexes, nanoparticles, and microparticles, as recited in **claims 86 and 94.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique carrier molecules capable of targeting an isolated DNA molecule with unique step properties and limitations that define the product made that do not extend one to the other.

9) naked DNA plasmid, a plasmid within a liposome, a retroviral vector, an AAV vector, or a recombinant adenoviral vector, as recited in **claim 90.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special

technical features for the following reasons: each of the species results in isolated polynucleotide vectors with unique step properties and limitations that define the product made that do not extend one to the other.

10) 3' UTRs, 5' UTRs, polyA sites and gene promoters, as recited in **claim 94.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique predetermined genomic sites with unique step properties and limitations that define the product made that do not extend one to the other.

11) a structural protein, an enzyme and a regulatory molecule, as recited in **claim 95.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique proteins with unique step properties and limitations that define the product made that do not extend one to the other. For example, structural proteins confer stiffness and rigidity to fluid biological components whereas enzymes are proteins that catalyze chemical reactions.

12) wild type Cre, CM1 Cre mutant, CM2 Cre mutant, as recited in **claims 98 and 101.**

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species results in unique proteins with

unique step properties and limitations that define the product made that do not extend one to the other.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: As the technical feature of polynucleotides and amino acid sequences linking the members do not constitute a special technical feature as defined by PCT Rule 13.2, particularly since each of the species does not share a substantially common structural feature, the requirement for unity of invention is not fulfilled.

Applicant is required, in reply to this action, to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, at least claims 72, 77, 86, 91 and 100 are generic.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633